

FLEBOGAMMA DIF - human immunoglobulin g injection, solution
Instituto Grifols, S.A.

Rx Only

DESCRIPTION

Immune Globulin Intravenous (Human), Flebogamma® 5% DIF (dual inactivation plus nanofiltration) (IGIV) is a sterile, clear or slightly opalescent and colorless to pale yellow, liquid ready to use, preparation of highly purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment and two sequential nanofiltrations through 35 nm and 20 nm pore size nanofilters connected in series.

Flebogamma® 5% DIF is a highly purified ($\geq 97\%$ IgG), unmodified, human IgG that contains the antibody specificities found in the donor population. IgG subclasses are fully represented with the following approximate percents of total IgG: IgG₁ is 66.6%, IgG₂, 28.5%, IgG₃, 2.7%, and IgG₄, 2.2% (1). Flebogamma® 5% DIF contains trace amounts of IgA (typically $< 50 \mu\text{g/mL}$) and IgM.

In the final formulation, Flebogamma® 5% DIF contains 5 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and $\leq 3 \text{ mg/mL}$ polyethylene glycol. There is no preservative in the formulation. The pH of the solution ranges from 5 to 6 and the osmolarity from 240 to 370 mOsm/L, which is within the normal physiologic range. The Fc and Fab functions are maintained in Flebogamma® 5% DIF.

All Source Plasma used in the manufacture of Flebogamma® 5% DIF was collected only at FDA approved plasmapheresis centers in the United States and tested by FDA-licensed serological tests and found to be non-reactive (negative) for Hepatitis B Surface Antigen (HBsAg), antibodies to Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) and negative on Nucleic Acid Test (NAT) for HCV and HIV. Additionally, NAT testing for the presence of HCV and HIV in the manufacturing plasma pool is also performed and found to be negative.

In addition, several manufacturing steps can contribute towards the safety of the final product. The effectiveness of these steps to remove or inactivate viruses from the product is evaluated through virus spiking experiments using a scaled version of the manufacturing process. Virus elimination experiments have been performed on 7 steps of the production process (1).

Flebogamma® 5% DIF production process includes the following specific virus inactivation/ removal steps:

- Pasteurization at 60 °C, 10 hours
- Solvent-Detergent treatment for 6 hours
- Double sequential nanofiltration through 35 nm and 20 nm filters

Pasteurization has been proved to achieve significant inactivation of both enveloped and non-enveloped viruses. Grifols has developed a pasteurization method (heat treatment at 60° C, 10 hours) using sorbitol as a stabilizer, which avoids denaturation of proteins and preserves antibody activity.

Solvent detergent treatment inactivates lipid coated viral contaminants such as HIV, HBV and HCV by destroying the lipid coat and the associated virus binding sites. By using this method, infection of the target cells and in-vivo virus replication is prevented.

Two sequential nanofiltrations through 35 nm and 20 nm pore size nanofilters are included in the production process, and they work to eliminate viruses by a specific size exclusion mechanism. This has been shown to be effective in removing by more than 4 log₁₀ the virus of the smallest size employed (porcine Parvovirus) by the smallest pore size filter (20 nm).

The following purification processes can eliminate or inactivate a theoretical viral load as well:

- Fraction I precipitation
- Fraction II+III precipitation
- 4% PEG precipitation
- pH 4 treatment for 4 hours at 37 °C

The viral reduction data (in log₁₀) from these experiments are summarized in Table 1.

Table 1. Flebogamma® 5% DIF Reduction Factors (RFs) and Overall Reduction Capacity (log₁₀/ml)

Target virus	HIV-1, HIV-2 (env. RNA)	HBV, Herpesvirus (env. DNA)		HCV (env. RNA)		WNV (env. RNA)	HAV (non-env. RNA)	B19 virus (non-env. DNA)
Model virus	HIV-1	PRV	IBR	BVDV	SINDBIS	WNV	EMC	PPV

Fraction I precipitation	<1.00*	nd	nd	nd	nd	2.78	nd	nd
Fraction II+III alcohol incubation	1.48	nd	nd	nd	nd	< 1.00*	nd	nd
4% PEG precipitation	≥ 6.10	≥ 5.92	nd	≥ 5.78	nd	nd	≥ 6.41	6.35
pH 4 treatment	2.47	≥ 5.32	nd	< 1.00*	nd	nd	1.36	na
Pasteurization	≥ 5.64	nd	≥ 6.33	nd	≥ 6.49	≥ 5.42	≥ 5.56	4.08
Solvent Detergent	≥ 4.61	≥ 6.95	nd	≥ 6.14	nd	≥ 5.59	na	na
Double nanofiltration (35 nm + 20 nm)	a	a	a	a	a	a	a	4.61
Overall Reduction Capacity	≥ 20.30	≥ 18.19	≥ 6.33	≥ 11.92	≥ 6.49	≥ 13.79	≥ 13.33	15.04

*When the RF is < 1 log₁₀/ml, it is not taken into account for the calculation of the overall reduction capacity.

≥: No residual infectivity detected / nd: not done / na: non-applicable, since the virus is theoretically resistant to this treatment.

a) During the nanofiltration validation, 9 different viruses (HIV, PRV, BVDV, WNV, EMC, SV40, BEV, Echo 11 and PPV) were evaluated. Eight of these viruses were inactivated by the process conditions and/or removed by prefiltration. Only PPV, the virus of smallest size, was affected neither by the filtration conditions nor by the prefiltration. Abbreviations: HIV; Human Immunodeficiency Virus, PRV; Pseudorabies Virus, IBR; Infectious Bovine Rhinotracheitis Virus, BVDV; Bovine Viral Diarrhoea Virus, SINDBIS; Sindbis virus, WNV; West Nile Virus, EMC; Encephalomyocarditis Virus, PPV; Porcine Parvovirus.

Acute toxicity studies were performed in mice and rats at doses up to 2.5 g/kg b.w. with infusion rates 6 to 30 times higher than the maximum rates recommended for humans. Although the NOAEL was not determined, no relevant adverse effects could be confirmed affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour of treated mice and rats. Five out of 25 rats treated with the highest dose at approximately 8 times the maximum infusion rate recommended for humans showed a transient “reddish urine” sign which was not confirmed as a relevant toxicity causing phenomenon after renal macro- and microscopical analysis. This phenomenon was associated to hemolysis when serum was analyzed, suggesting a possible relation to cross reactivity of rodent red cells with human antibodies. No “reddish urine” was detected in any mouse, a much smaller animal where the rate of infusion was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any renal alteration either.

CLINICAL PHARMACOLOGY

Flebogamma® 5% DIF was administered as an IV infusion (300 to 600 mg/kg) to subjects with primary humoral immunodeficiency disease (PID) every 3 (n = 8) or 4 (n = 12) weeks for 12 months. The pharmacokinetics of total IgG was determined after the 7th infusion for the 3-week dosing interval and after the 5th infusion for the 4-week dosing interval (Table 2).

Table 2. Pharmacokinetic Variables of Total IgG in Patients with PID

Variable	3-Week Dosing Interval (n = 8)		4-Week Dosing Interval (n = 12)	
	Mean	SD	Mean	SD
C_{max} (mg/dL)	1929	441	2069	338
	[1300 - 2420]^a		[1590 - 2800]	
AUC_{0-∞} (day·mg/dL)	31159	6572	32894	3886
	[20458 - 40104]		[27650 - 41814]	
Clearance (mL/day)	139	57	109	33
	[81 - 243]		[59 - 161]	
Half-life (days)^c	30	9	32	5
	[19 - 41]		[25 - 39]	
Trough IgG level (mg/dL)^b	951.38	132.42	899.89	92.03
	[773.17 - 1143.15]		[776.70 - 1137.14]	

a. The numbers in brackets are the minimum and maximum values.

b. For subjects on the 3-week schedule, the average of the trough levels from Infusion 7 to the end of the study was calculated; for those on a 4-week schedule, the average of the trough levels from Infusion 5 to the end of the study was calculated. The means of the subject means are presented in this table.

c. This half-life is an apparent value derived from a period of measurement of 28 days.

Pharmacokinetic data for antibodies to specific antigens are in Table 3.

Table 3. Summary of Pharmacokinetic Data for Antibodies to Specific Antigens

Test (unit)	Statistic	3-Week Dosing Interval (n = 8)			4-Week Dosing Interval (n = 12)		
		Cmax	Trough	Half-life (days)	Cmax	Trough	Half-life (days)
<i>S. pneumoniae</i> Type 14 (µg/mL)	Mean (SD)	14 (4)	6 (4)	16 (6)	16 (6)	6 (2)	41 (29)
	Min-Max	9 - 22	2 - 18	12 - 23	8 - 33	3 - 10	12 - 78
<i>S. pneumoniae</i> Type 19F (µg/mL)	Mean (SD)	11 (3)	5 (7)	16 (6)	13 (4)	4 (1)	30 (28)
	Min-Max	8 - 19	1 - 25	11 - 25	6 - 22	2 - 6	11 - 83
<i>S. pneumoniae</i> Type 4 (µg/mL)	Mean (SD)	3 (1)	1 (0.4)	14 (5)	4 (1)	1 (1)	41 (29)
	Min-Max	2 - 5	0 - 2	10 - 20	2 - 6	0 - 2	14 - 86
<i>S. pneumoniae</i> Type 6B (µg/mL)	Mean (SD)	13 (3)	4 (2)	16 (4)	14 (5)	4 (1)	32 (20)
	Min-Max	7 - 17	1 - 9	12 - 20	7 - 25	2 - 7	15 - 60
<i>S. pneumoniae</i> Type 9V (µg/mL)	Mean (SD)	6 (2)	4 (2)	14 (4)	7 (2)	4 (1)	28 (19)
	Min-Max	4 - 10	1 - 8	10 - 18	3 - 11	2 - 6	13 - 55
Tetanus Antitoxoid Antibody (IU/mL)	Mean (SD)	9 (2)	5 (2)	28 (13)	10 (3)	5 (1)	24 (13)
	Min-Max	7 - 11	2 - 8	11 - 45	5 - 14	3 - 6	9 - 51

There is evidence that the half-life of IgG can vary considerably among patients (2 - 5).

There were 3 adolescent (≤ 16 years of age) subjects who underwent pharmacokinetic testing, all of whom were on the 3-week infusion schedule. There were no clinically relevant differences among the adults and adolescents that were tested.

Clinical Studies:

Grifols study IG-201 was a multicenter, open-label, historically controlled study conducted in the United States. A total of 46 subjects with primary humoral immune deficiency diseases aged 15 - 75 years (63% male, 37% female) were enrolled, and their data were analyzed for safety, pharmacokinetics and efficacy. Subjects were treated with Flebogamma® 5% DIF at a dose of 300 - 600 mg/kg per infusion every 3 or 4 weeks for 12 months. The primary efficacy variable was the annualized number of acute serious bacterial infections: bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses and bacterial meningitis. The secondary efficacy variables were the number of days of work/school missed, the number of hospitalizations and the number of days of each hospitalization, the number of visits to physicians or emergency rooms, the number of other infections documented by positive radiographic findings and fever, and the number of days of therapeutic and prophylactic oral and parenteral antibiotic use.

The results showed that subjects had a serious acute bacterial infection rate of 0.021 infections/subject/year (98% confidence interval = 0.001 to 0.112), a rate that is much less than 1 infection/subject/year (Table 4).

Table 4. Summary of Bacterial Infections (Intent-to-Treat Population, N=46)

Infection	Patients		Total Episodes	Estimated Rate [1]	98% Confidence Interval [2]
	N	%			
Bacterial Pneumonia	1	2.2	1		
Bacteremia or Sepsis	0	0	0		
Osteomyelitis/Septic Arthritis	0	0	0		
Bacterial Meningitis	0	0	0		
Total Patients	1	2.2	1	0.021	0.001-0.112

[1] Estimate = total episodes/total patient years

[2] The confidence interval is obtained by using a generalized linear model procedure for Poisson distribution

The secondary efficacy endpoints were annualized by using the subject-years exposure data only of those subjects experiencing the endpoints, not of the entire study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days / subject/year (Table 5).

Table 5. Summary of Secondary Efficacy Variables

Variable	Subjects		Mean number of events, days or visits/subject/year
	n	%	
Work/school days missed	23	50.0	12.95
Days of normal activities missed	18	39.1	7.28
Days in hospital	4	8.7	0.77
Visits to physician/ER	29	63.0	4.31
Number of other validated infectious episodes	33	71.7	1.96
Days of therapeutic oral antibiotic use	35	76.1	55.52
Days of therapeutic parenteral antibiotic use	2	4.3	0.14
Days of other therapeutic antibiotic use	16	34.8	44.30
Days of prophylactic oral antibiotic use	19	41.3	81.08
Days of prophylactic parenteral antibiotic use	1	2.3	0.02
Days of other prophylactic antibiotic use	0	0.0	0.00

a. Estimate = Total days or visits/total subject years.

b. The 95% confidence intervals were obtained by using a generalized linear model procedure for Poisson distribution.

The dosing statistics for this study are in Table 6.

Table 6. Statistical Summary of the Mean Total Dose (mg/kg) of Flebogamma® 5% DIF Administered Per Infusion

Statistic	3-Week Dosing Interval	4-Week Dosing Interval	Total
n	13	33	46
Mean (SD)	451 (98.72)	448 (81.93)	449 (85.96)
Median	440	453	449
Q1, Q3 ^a	384.2, 540.5	379.5, 511.1	380.9, 518.8
Min, Max	288.4, 588.2	298.2, 591.1	288.4, 591.1

a. Q1 is the 25th percentile, and Q3 is the 75th percentile.

INDICATIONS AND USAGE

Flebogamma® 5% DIF is indicated for replacement therapy in primary (inherited) humoral immunodeficiency disorders, such as common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome. Flebogamma® 5% DIF is especially useful when rapid replacement of IgG or the attainment of high serum levels of IgG is desired.

CONTRAINDICATIONS

Flebogamma® 5% DIF should not be administered to individuals with a history of severe or anaphylactic reactions to blood or blood-derived products. Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using Flebogamma® 5% DIF even though it contains low amounts of IgA (typically < 50 µg/mL). These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immune globulin is clearly indicated. Such patients should only receive intravenous immune globulin with utmost caution and in a setting where supportive care is available for treating life-threatening reactions. If patients are known to be intolerant to any component of Flebogamma® 5% DIF, such as sorbitol (i.e., intolerance to fructose), they should not receive the product.

WARNINGS

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death (6). Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute

renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Flebogamma® 5% DIF does not contain sucrose. See PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. The risk that such products will transmit an infectious agent has been greatly reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. (See DESCRIPTION section). Plasma pools for manufacture are screened using Nucleic Acid Testing with polymerase chain reaction technology for HIV and HCV. Seven steps in the manufacturing process have been evaluated and demonstrated to provide relevant reductions for all the tested viruses. Despite these measures, such IGIV products can still potentially transmit disease. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 888-GRIFOLS (888-474-3657). Physicians should discuss the potential risks and benefits of the use of this product with the patient.

All patients, but especially individuals receiving Flebogamma® 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at risk for the development of inflammatory reactions characterized by fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding information in the DOSAGE AND ADMINISTRATION section may reduce the risk of these types of events.

Appropriate supportive care, including immediate access to epinephrine injection, should be available for the management of acute anaphylactic reactions.

PRECAUTIONS

General:

Any vial that has been entered should be used promptly. Partially used vials should be discarded and not saved for future use because the solution contains no preservative. Do not use if turbid. Solution that has been frozen should not be used.

Ensure that patients are not volume-depleted before the initiation of the infusion of IGIV.

Renal Function:

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure (6). Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma® 5% DIF and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing Flebogamma® 5% DIF at a maximum rate less than 0.06 mL/kg (3 mg/kg) body weight/minute.

Aseptic Meningitis Syndrome:

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic milliliter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high-dose (e.g., >1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae (7 - 10).

Hemolysis:

Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis (11 - 13). Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (14) [See ADVERSE REACTIONS]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See PRECAUTIONS: Laboratory Tests].

Thrombotic Events:

Thrombotic events have been reported in association with IGIV (15 - 17) (See ADVERSE REACTIONS). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at

risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See PRECAUTIONS: Laboratory Tests].

Transfusion-Related Acute Lung Injury (TRALI):

There have been reports of non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV (18). TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum [See PRECAUTIONS: Laboratory Tests].

Information for Patients:

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

It is recommended that the lot number of the vials used be recorded when Flebogamma[®] 5% DIF is administered.

Laboratory Tests:

Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma[®] 5% DIF in patients judged to have a potential increased risk for developing acute renal failure and again at appropriate intervals thereafter.

Following infusion of Flebogamma[®] 5% DIF, there may be a transitory rise of various antibody titers that may result in misleading positive results in serological testing.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum.

Pregnancy Category C:

Animal reproduction studies have not been performed with Flebogamma[®] 5% DIF. It is also not known whether Flebogamma[®] 5% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma[®] 5% DIF should be given to a pregnant woman only if clearly needed.

Drug Interactions:

Antibodies in Flebogamma[®] 5% DIF may interfere with the response to live viral vaccines, such as measles, mumps, and rubella. Physicians should be informed of recent therapy with Immune Globulin Intravenous (Human) so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IGIV administration.

Pediatric Use:

The above mentioned clinical trial with Flebogamma[®] 5% DIF enrolled only a very limited number of children (0) and adolescents (3) with primary humoral immune deficiency, a number insufficient to fully characterize the efficacy and safety in pediatric patients.

Although preliminary safety data in children and adolescents with primary humoral immune deficiency who received Flebogamma[®] 5% DIF has not revealed differences between the safety profiles of the product in pediatric and adult patients, the experience has been too limited to consider the safety and efficacy of Flebogamma[®] 5% DIF to be established in children and adolescents.

Geriatric Use:

Subjects over 65 are at increased risk of renal failure with IGIV treatment. For these subjects, and for any other subjects at risk of renal failure, the infusion rate of Flebogamma[®] 5% DIF should be limited to < 0.06 mL/kg/min (3 mg/kg/min). Clinical trial IG-201 had only a limited number of subjects over the age of 65 enrolled (3), and therefore, the information available on them is limited.

ADVERSE REACTIONS

Increases of creatinine and blood urea nitrogen (BUN) have been observed as soon as 1 to 2 days following infusion of IGIV. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment (19). Types of severe renal adverse reactions that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis (20), proximal tubular nephropathy, and osmotic nephrosis (6).

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate [See DOSAGE AND ADMINISTRATION] must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Adverse reactions may occur more frequently when a high infusion rate is used, the treatment is the initial exposure to immunoglobulin, the immunoglobulin product has been changed to that of a different manufacturer, or there has

been a long interval (more than 8 weeks) since the previous infusion. Slowing or stopping an infusion usually results in the prompt disappearance of symptoms.

Post-marketing:

The following adverse reactions have been identified and reported during the post-approval use of IGIV products (21).

Respiratory	Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular	Cardiac arrest, thromboembolism, vascular collapse, hypotension
Neurological	Coma, loss of consciousness, seizures, tremor
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, bullous dermatitis
Hematologic	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
General/Body as a Whole	Pyrexia, rigors
Musculoskeletal	Back pain
Gastrointestinal	Hepatic dysfunction, abdominal pain

Because post-marketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

Adverse events were reported in a study of 46 individuals with primary humoral immunodeficiency diseases receiving infusions every 3 to 4 weeks of 300 to 600 mg/kg body weight. Forty-three (94%) subjects experienced at least 1 adverse event irrespective of the relationship with the product, and these subjects reported a total of 595 adverse events. None of the 46 subjects who participated in this study discontinued the study prematurely due to an adverse experience related to the study drug. One subject had treatment-emergent bronchiectasis, mild, ongoing, after infusion #10; and one subject had recurrent moderate leukopenia after the 7th and 12th infusions.

Adverse events that occurred with an incidence of > 15% on a per subject basis are summarized in Table 7. No adverse events occurred with an incidence of > 2% on a per infusion basis.

Table 7. Adverse Events Occurring with an Incidence of > 15%

Adverse Event	Number of AEs	Number of Subjects with AEs	Percent of Subjects with AEs
Combined Bronchitis	19	14	30
Cough and productive cough	10	10	22
Diarrhoea NOS ^a	14	9	20
Headache NOS and sinus headache	46	16	35
Nasal congestion	11	7	15
Injection site reaction NOS	13	7	15
Pyrexia	27	17	37
Arthralgia	11	7	15
Sinusitis NOS	38	20	44
Pharyngitis	9	8	17
Upper Respiratory tract infection	24	15	33
Wheezing and asthma aggravated	24	10	22

a. NOS = not otherwise specified.

The total number of AEs (regardless of attribution) reported whose onset was within 72 hours after the end of an infusion of Flebogamma[®] 5% DIF was 216. There were a total of 709 infusions, resulting in a rate of 0.305 (95% confidence interval 0.225 to 0.412) temporally associated AEs per infusion. There were 144 infusions (20.1%, 1-sided 95% upper bound confidence interval = 24.4%) associated with 1 or more AEs that began within 72 hours after the completion of an infusion.

A summary of infusions with mild, moderate, and severe treatment-related adverse events is in Table 8.

Table 8. Summary of Infusions with Mild, Moderate, and Severe Treatment-Related Adverse Events

Severity of AE	No. Infusions with AE	Adjusted % ^a	Confidence Interval ^b
Mild	58	7.9	10.4

Moderate	25	3.6	4.9
Severe	1	0.1	0.3

a. Adjusted % = average of the % of infusions with a treatment-related adverse event for each individual subject.

b. The 95% upper bound for the adjusted % of infusions for which at least 1 treatment-related adverse event was reported was derived by using the t-statistic.

The number and percent of subjects with treatment-emergent rises in AST or ALT are in Table 9.

Table 9. Number (%) of Subjects with Treatment-Emergent Rises in AST or ALT (N = 46)

Laboratory Test	Assessment Criteria	n	%
AST	Above 3x the ULN^a	3	6.5
ALT	Above 3x the ULN	1	2.2

a. ULN = upper limit of normal.

None of these subjects had a concomitant treatment-emergent rise in total bilirubin.

Reported adverse reactions with Flebogamma[®] 5% DIF and other IGIV products include: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema, often beginning within 60 minutes of the start of the infusion.

Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented.

DOSAGE AND ADMINISTRATION

The usual dose of Flebogamma[®] 5% DIF for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight administered every 3 to 4 weeks. Doses may be adjusted over time to achieve the desired trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.

An in-line filter with a pore size of 15 to 20 microns is recommended for the infusion. Antibacterial filters (0.2 micron) may also be used, although they may slow infusions. Discard unused contents and administration devices after use.

The infusion of Flebogamma[®] 5% DIF should be initiated at a rate of 0.01 mL/kg body weight/minute (0.5 mg/kg/minute). If, during the first 30 minutes, the patient does not experience any discomfort, the rate may be gradually increased to a maximum of 0.10 mL/kg/minute (5 mg/kg/minute).

For patients judged to be at risk for developing renal dysfunction or considered to be at increased risk of thrombotic/thromboembolic events, it may be prudent to limit the amount of product infused per unit time by infusing Flebogamma[®] 5% DIF at a maximum rate less than 0.06 mL/kg body weight/minute (3 mg/kg/minute). No prospective data are available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded, and the concentration and infusion rate should be the minimum level practicable. Reduction in dose, concentration, and/or rate of infusion in patients at risk of acute renal failure, which includes patients over 65 [See WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS] has been proposed in the literature in order to reduce the risk of acute renal failure (22).

Compatibility Issues:

Flebogamma[®] 5% DIF should be inspected visually for particulate matter and color prior to administration, if particles are detected the vial shall not be used. Do not use if turbid. If large doses are to be administered, several vials of Flebogamma[®] 5% DIF may be pooled into an empty sterile IV solution container by using aseptic technique. Dilution with IV fluids is not recommended. Injection of other medications into an IV tubing being used for Flebogamma[®] 5% DIF is not recommended.

Specific drug interactions and incompatibilities have not been studied. Flebogamma[®] 5% DIF should be infused through a separate intravenous line. Do not add any medications or IV fluids to the Flebogamma[®] 5% DIF infusion container. Do not mix IGIV products of different formulations or from different manufacturers.

HOW SUPPLIED

Flebogamma[®] 5% DIF is supplied in the following vial sizes:

NDC Number	Size	Grams IgG
61953-0004-1	10 mL	0.5
61953-0004-2	50 mL	2.5
61953-0004-3	100 mL	5.0

61953-0004-4	200 mL	10.0
61953-0004-5	400 mL	20.0

STORAGE

Store at +2 to +25° C (36 to 77° F). Do not freeze. Discard after expiration date.

REFERENCES

1. Data on file. Instituto Grifols, S.A.
2. Waldmann TA, Strober W. Metabolism of immunoglobulins. *Prog Allergy* 1969; 13:1-110.
3. Morrell A, Riesen W. Structure, function and catabolism of immunoglobulins. In: Nydegger UE, editor. Immunohemotherapy. London: Academic Press; 1981, p. 17-26.
4. Stiehm ER. Standard and special human immune serum globulins as therapeutic agents. *Pediatrics* 1979; 63:301-19.
5. Buckley RH. Immunoglobulin replacement therapy: indications and contraindications for use and variable IgG levels achieved. In: Alving BM, Finlayson JS, editors. Immunoglobulins: characteristics and use of intravenous preparations. Washington DC: US Department of Health and Human Services; 1979, p. 3-8.
6. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc Nephrol* 1997; 8:1788-94.
7. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; 121:259-62.
8. Kato E, Shindo S, Eto Y, et al. Administration of immune globulin associated with aseptic meningitis. *JAMA* 1988; 259:3269-71.
9. Casteels-Van Daele M, Wijndaele L, Hanninck K, et al. Intravenous immune globulin and acute aseptic meningitis. *N Engl J Med* 1990; 323:614-5.
10. Scribner CL, Kapit RM, Phillips ET, et al. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med* 1994; 121:305-6.
11. Copelan EA, Strohm PL, Kennedy MS, et al. Hemolysis following intravenous immune globulin therapy. *Transfusion* 1986; 26:410-2.
12. Thomas MJ, Misbah SA, Chapel HM, et al. Hemolysis after high-dose intravenous Ig. *Blood* 1993; 15:3789.
13. Reinhart WH, Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet* 1992; 339:662-4.
14. Kessary-Shoham H, Levy Y, Shoenfeld Y, et al. In vivo administration of intravenous immunoglobulin (IVIg) can lead to enhanced erythrocyte sequestration. *J Autoimmun* 1999; 13:129-35.
15. Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994; 44:223-6.
16. Woodruff RK, Grigg AP, Firkin FC, et al. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 1986; ii:217-8.
17. Wolberg AS, Kon RH, Monroe DM, et al. Coagulation factor XI is a contaminant in intravenous immunoglobulin preparations. *Am J Hematol* 2000; 65:30-4.
18. Rizk A, Gorson KC, Kenney L, et al. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001; 41:264-8.
19. Winward DB, Brophy MT. Acute renal failure after administration of intravenous immunoglobulin: review of the literature and case report. *Pharmacotherapy* 1995; 15:765-72.
20. Phillips AO. Renal failure and intravenous immunoglobulin. *Clin Nephrol* 1992; 37:217.
21. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003; 17:241-51.

22. Tan E, Hajinazarian M, Bay W, et al. Acute renal failure resulting from intravenous immunoglobulin therapy. *Arch Neurol* 1993; 50:137-9.

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Revised: November 2006.

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 10 ML VIAL

NDC 61953-0004-1

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 0.5 g

0.5 g in 10 mL Rx only.

Store at 2 – 25 °C (36 – 77 °F).

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 50 ML VIAL

NDC 61953-0004-2

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 2.5 g

2.5 g in 50 mL Rx only.

Dosage and directions for administration, see package insert.

Store at 2 – 25 °C (36 – 77 °F). DO NOT USE IF TURBID. ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 100 ML VIAL

GRIFOLS

NDC 61953-0004-3

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 5 g

5 g in 100 mL Rx only.

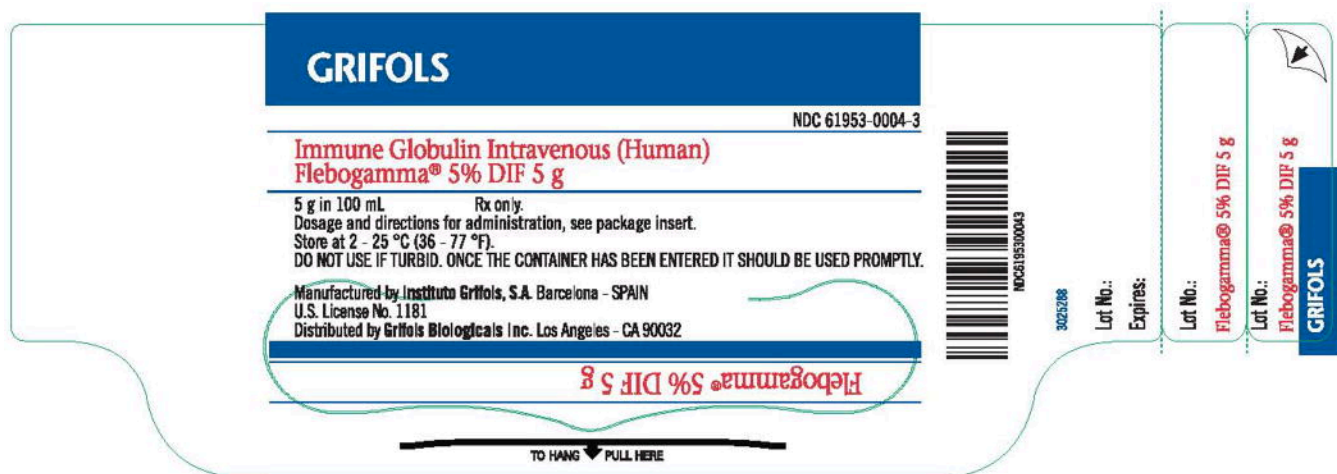
Dosage and directions for administration, see package insert.

Store at 2 – 25 °C (36 – 77 °F).

DO NOT USE IF TURBID. ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 200 ML VIAL

GRIFOLS

NDC 61953-0004-4

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 10 g

10 g in 200 mL Rx only.

CONTENTS: Each 200 mL contains Immune Globulin (Human) 10 g; D-sorbitol 10 g; Protein contents is 50g/L

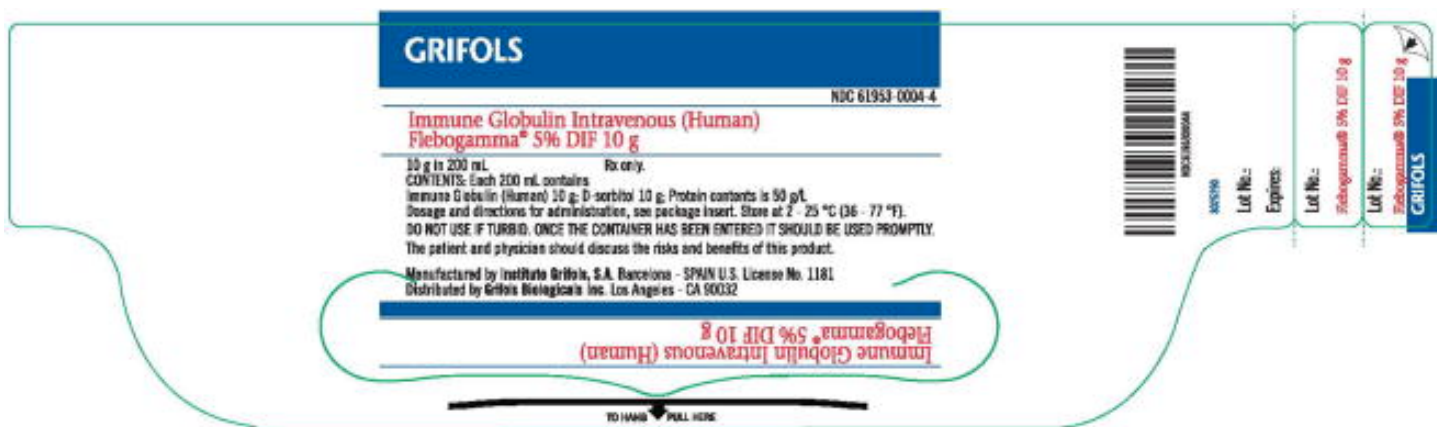
Dosage and directions for administration, see package insert. Store at 2 – 25 °C (36 – 77 °F).

DO NOT USE IF TURBID. ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.

The patient and physician should discuss risks and benefits of this product.

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 400 ML VIAL

GRIFOLS

NDC 61953-0004-5

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 20 g

20 g in 400 mL Rx only.

CONTENTS: Each 400 mL contains Immune Globulin (Human) 20 g; D-sorbitol 20 g; Protein contents is 50g/L

Dosage and directions for administration, see package insert. Store at 2 – 25 °C (36 – 77 °F).

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.

The patient and physician should discuss risks and benefits of this product.

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PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 10 ML CARTON

GRIFOLS

NDC 61953-0004-1

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 0.5 g

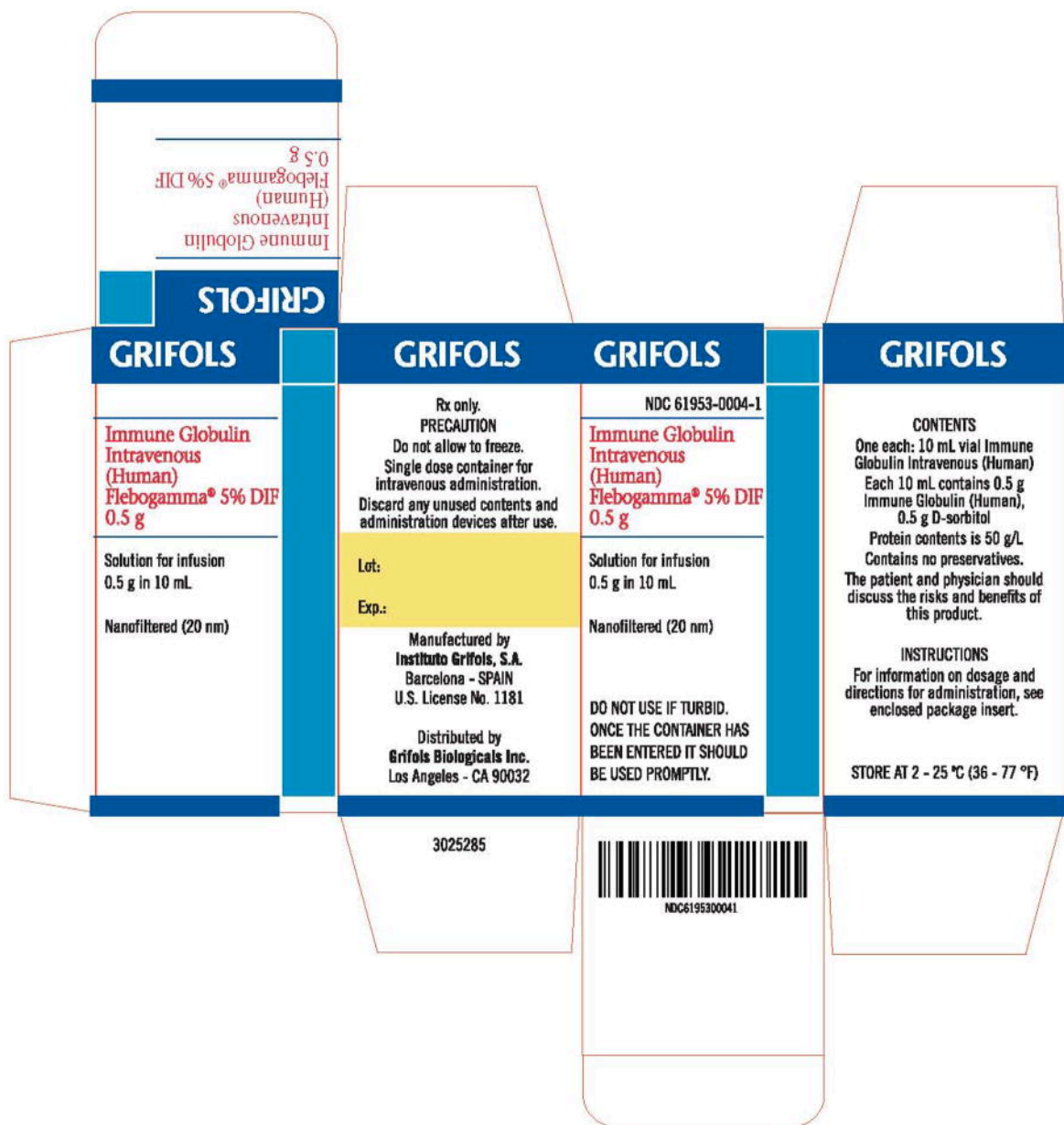
Solution for infusion

0.5 g in 10 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.



PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 50 ML CARTON
GRIFOLS

NDC 61953-0004-2

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 2.5 g

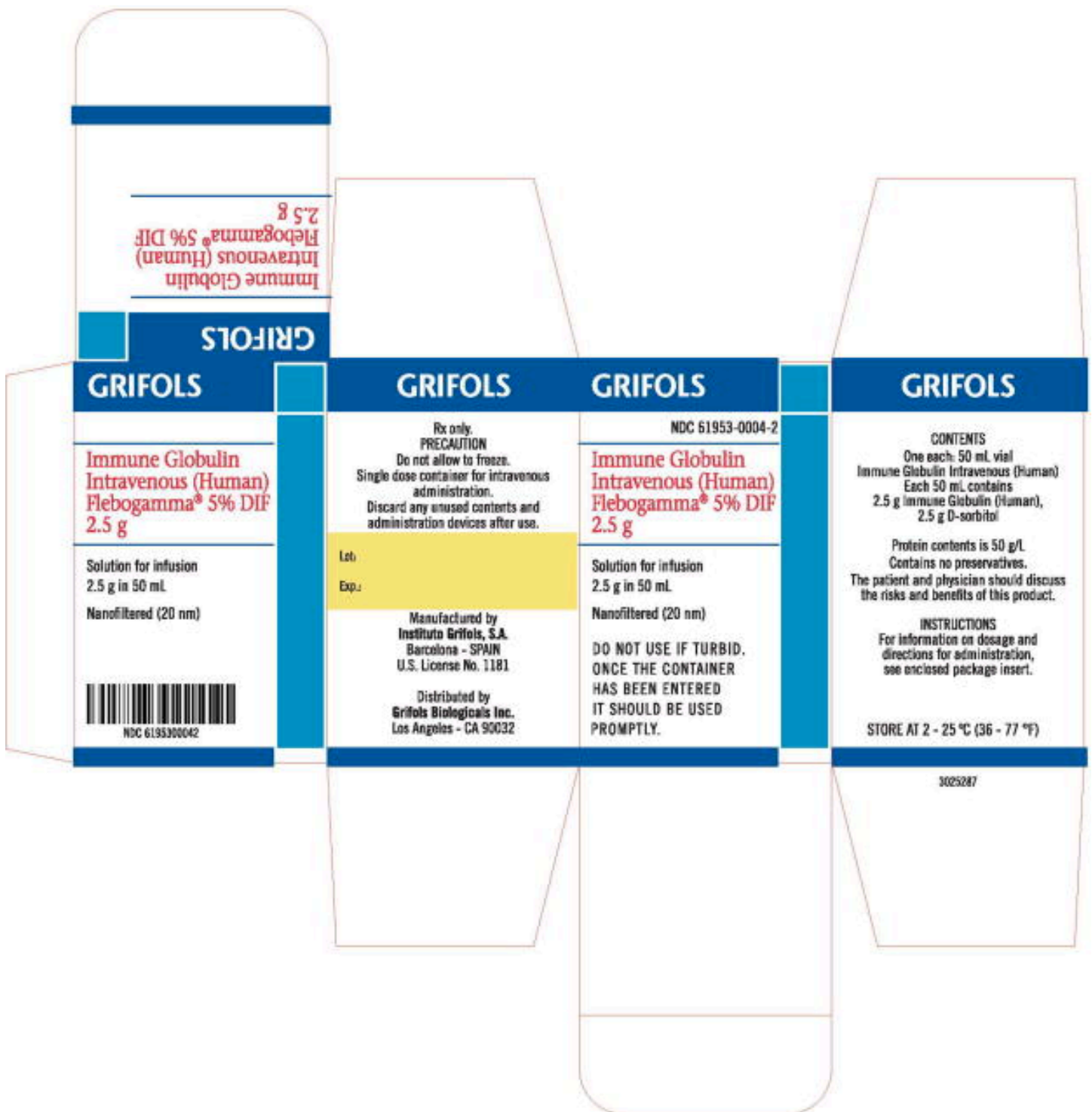
Solution for infusion

2.5 g in 50 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.



PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 100 ML CARTON

GRIFOLS

NDC 61953-0004-3

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 5 g

Solution for infusion

5 g in 100 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.



PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 200 ML CARTON

GRIFOLS

NDC 61953-0004-4

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 10 g

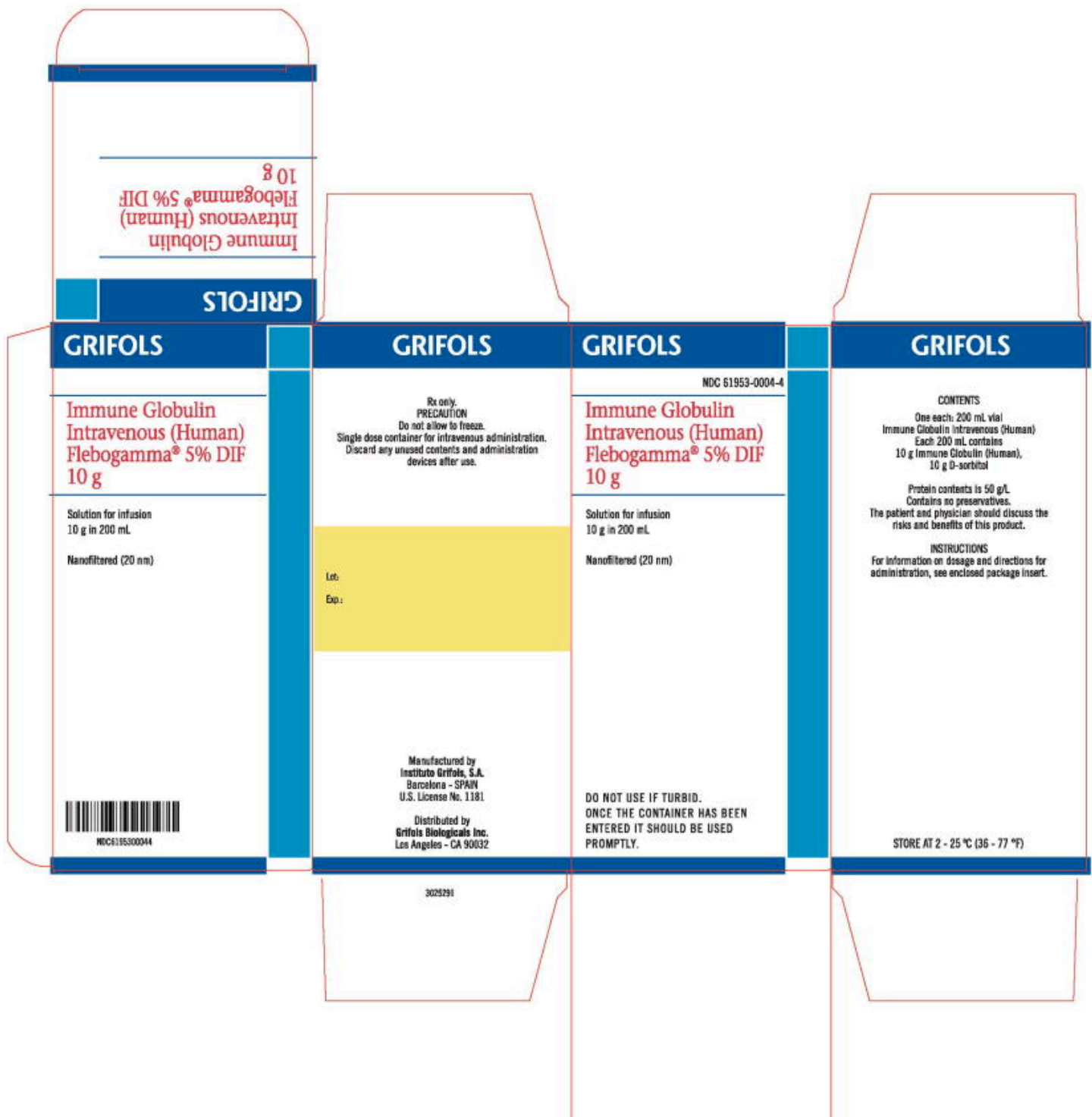
Solution for infusion

10 g in 200 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.



PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 400 ML CARTON
GRIFOLS

NDC 61953-0004-5

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF 20 g

Solution for infusion

20 g in 400 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.

ONCE THE CONTAINER HAS BEEN ENTERED IT SHOULD BE USED PROMPTLY.

Immune Globulin
Intravenous (Human)
Flebogamma® 5% DIF
20 g

GRIFOLS

GRIFOLS

Immune Globulin
Intravenous (Human)
Flebogamma® 5% DIF
20 g

Solution for infusion
20 g in 400 mL

Nanofiltered (20 nm)



NDC61953-0004-5

GRIFOLS

Rx only.
PRECAUTION
Do not allow to freeze.
Single dose container for intravenous
administration.
Discard any unused contents
and administration devices after use.

Lot:
Exp.:

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NDC 61953-0004-5

Immune Globulin
Intravenous (Human)
Flebogamma® 5% DIF
20 g

Solution for infusion
20 g in 400 mL

Nanofiltered (20 nm)

DO NOT USE IF TURBID.
ONCE THE CONTAINER HAS
BEEN ENTERED IT SHOULD BE
USED PROMPTLY.

GRIFOLS

CONTENTS
One each: 400 mL vial
Immune Globulin Intravenous (Human)
Each 400 mL contains
20 g Immune Globulin (Human),
20 g D-sorbitol

Protein contents is 50 g/L
Contains no preservatives.
The patient and physician should discuss
the risks and benefits of this product.

INSTRUCTIONS
For information on dosage and directions
for administration, see enclosed package insert.

STORE AT 2 - 25 °C (36 - 77 °F)

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